McCune-Albright syndrome: new insights

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McCune-Albright syndrome is a rare disease caused by an activating mutation in the gene for the G protein subunit ($G_s\alpha$) that stimulates cellular cyclic AMP formation. The mutation occurs early during embryogenesis and results in a variable constellation of abnormalities involving bone, skin, endocrine glands, and other tissues. Although traditionally regarded as a disease of children, clinical manifestations may progress into adulthood. Efforts are being made to define the precise mechanisms by which inappropriate $G_s\alpha$ activation affects cellular proliferation and differentiated function and to develop more effective means to treat fibrous dysplasia of bone. Curr Opin Endocrinol Diabetes 1999, 6:119–125

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Abbreviations

cAMP	cyclic AMP
FD	fibrous dysplasia
G_s	stimulatory G protein
IL-6	interleukin-6
MAS	McCune-Albright syndrome
PHP	pseudohypoparathyroidism
PKA	protein kinase A

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McCune-Albright syndrome (MAS) is a sporadic disease classically defined by polyostotic fibrous dysplasia (FD), café-au-lait spots, sexual precocity, and other hyperfunctional endocrinopathies. Endocrine tissues that function autonomously in MAS include the gonads, thyroid, adrenal cortex, and pituitary somatotrophs. The fact that cAMP was known to promote the growth or function of these tissues led to the discovery that MAS was caused by heterozygous somatic mutations of codon 201 in the gene encoding the α subunit of the stimulatory G protein (G_s). Mutations at this position inhibit GTPase activity and lead to constitutive activity. The timing of the mutational event during early development produces cellular mosaicism.

This review focuses on recent advances in our understanding of the pathophysiology and treatment of MAS, and will not attempt to be comprehensive. The interested reader is referred to several excellent reviews on this subject [1–3, 4••].

Mutation detection

With one exception [5], $G_s\alpha$ mutations encoding substitution of Arg^{201} with either Cys or His have been found in all MAS patients where affected tissue was available for molecular analysis. No difference in the phenotype associated with Cys or His has been reported. An Arg^{201} to Ser mutation was recently detected in a single patient with panostotic fibrous dysplasia [6•], suggesting that this particular substitution may have a different effect. Mutations of Gln^{227} have been detected in isolated endocrine tumors, but have not been found in MAS. Substitutions at codon 227 are more activating than those at codon 201 [7,8••] and may therefore have a lethal effect on embryonic cells even when expressed in the mosaic state.

The fact that mutant alleles are detected in variable abundance in different tissues from the same MAS patient validates the somatic mosaic model, but complicates the process of molecular diagnosis. Even severely affected patients show little evidence of mutation in DNA prepared from blood leukocytes. A variety of different methods have been used to detect $G_s\alpha$ mutations in tissue samples [9–11,12••], but in all cases taking the time to identify a region containing a high proportion of abnormal cells is an important initial step. Bone specimens must not be decalcified in acidic solution [11]. A non-radioactive technique that employs sequential rounds of PCR and endonuclease digestion to

selectively amplify rare mutant alleles has recently been adapted for the detection of Arg^{201} mutations [6•]. As with all PCR-based methods, special care must be taken to avoid artifacts.

Clinical manifestations and treatment

Abnormalities due to activating $G_s\alpha$ mutations (*gsp*) occur alone or in combination in individual patients and range in severity from subclinical laboratory abnormalities to incapacitating disease. Although most MAS patients manifest only classical features of the syndrome, a subset of patients exhibit other significant non-endocrine findings, including hepatobiliary and cardiovascular abnormalities [10] and intramuscular myxomas [13]. Severe disease may be associated with an earlier mutational event that leads to a widespread distribution of mutant cells in the embryo, while incomplete forms of MAS may result from a mutation that occurs later in embryologic development. A focal somatic mutation of the same $G_s\alpha$ gene even later in life is associated with diseases that involve only a single tissue, such as somatotroph or thyroid tumors [7,9,14,15], monostotic fibrous dysplasia [16], isolated ovarian cysts [17•], or Leydig cell tumors [18].

Endocrine

Sexual precocity in girls with MAS is related to estrogen production by hyperfunctional ovarian cysts, and has been treated with the aromatase inhibitor testolactone or with medroxyprogesterone [4••]. It has been reported that testolactone can interfere with androgen measurements in certain serum radioimmunoassays, yielding spuriously high values [19]. A recent clinical trial with the potent aromatase inhibitor fadrozole failed to demonstrate a beneficial effect [20], but newer inhibitors such as letrozole and arimidex may eventually prove more useful. There is one case report demonstrating the effectiveness of the antiestrogen tamoxifen in treating the precocious puberty of MAS in a girl who did not respond to high doses of testolactone [21•]. Long-term efficacy and safety in a larger population remain to be established. MAS girls with bone ages greater than 11 years can develop secondary central precocious puberty and will benefit from additional therapy with a long acting GnRH agonist [4••,21•,22]. Some women with MAS achieve normal menses and fertility, but others have persistence of autonomous gonadal activity and experience irregular menstrual cycles, metrorrhagia, and other gynecological problems [23,24, Unpublished observations]. It is possible that women with MAS are at increased risk for developing breast cancer due to early and intense estrogen exposure [2] and/or the presence of *gsp* mutations in the breast [Unpublished observations].

Thyroid disease is the second most common endocrinopathy in MAS [4••,25•,26]. Abnormalities (including goiter, cysts, nodules, and hyperthyroxinemia) are found in 30% to 40% of MAS patients, and often follow an indolent course. We are aware of only a single MAS adult who has developed thyroid carcinoma (Unpublished data). *Gsp* mutations have been identified in a small fraction of isolated human thyroid carcinomas [9,27], and activating the cAMP cascade in thyrocytes of transgenic mice leads to thyroid hyperplasia and hyperthyroxinemia, but appears insufficient to promote malignant growth [28,29]. Some investigators have recently questioned the precise role that mutational activation of the cAMP pathway plays in the evolution of human thyroid neoplasia [30,31]. One possibility is that *gsp* mutations represent an infrequent early event in the neoplastic process, with progression dependent on accumulation of additional genetic abnormalities. In addition, the low incidence of thyroid neoplasia in MAS patients may be related to the fact that affected children are often treated with radioiodine or thyroidectomy [25•].

GH hypersecretion due to somatotroph hyperplasia or adenoma is an uncommon manifestation of MAS that has been treated successfully with octreotide, a long-acting somatostatin analogue [32]. Studies designed to determine whether *gsp*-positive somatotroph tumors in non-MAS patients have a different clinical phenotype than *gsp*-negative tumors have produced conflicting results, but tumor cells expressing the *gsp* mutation do appear to have higher sensitivity to the inhibitory action of octreotide, perhaps due to a cAMP-mediated increase in somatostatin receptor expression [33]. Somatostatin receptor scintigraphy in one MAS patient with acromegaly failed to reveal the presence of adenoma; however, increased uptake of radioligand was seen in areas of dysplastic bone [34].

Cushing's syndrome and hyperparathyroidism are other rare endocrine manifestations of MAS [2]. Several cases of isolated primary hyperparathyroidism associated only with FD have been reported. Failure to detect *gsp* mutations in dysplastic bone or parathyroid adenoma from one such patient raises the possibility that this represents a syndrome distinct from MAS [35,36].

Hyperphosphaturic hypophosphatemia with accompanying rickets or osteomalacia is a complication in some cases of MAS. Initial reports of hypophosphatemia in MAS suggested that it was a rare occurrence. More recent reports suggest that some degree of renal phosphate wasting may be the norm [37,38]. The etiology of the renal phosphate wasting is not clear. Some authors have found evidence of a proximal renal tubule defect presumably due to the presence of the $G_s\alpha$ mutation [37]. Others believe it is the result of elaboration of a phosphaturic compound from the FD lesions, as is seen in oncogenic osteomalacia. The possibility exists that it

is a combination of the two. Renal phosphate wasting can occur in the presence of a normal serum phosphate, especially early in the course of the condition. For this reason screening only serum phosphate is inadequate. Evaluation of hyperphosphaturia should include a calculation of the tubular maximum of phosphate to glomerular filtration rate ratio (TmP/GFR). If phosphate wasting is present, treatment with phosphate and 1,25-dihydroxyvitamin D_3 should be considered.

Bone

The destructive lesions of FD are characterized by the progressive replacement of the normal architecture of bone with abnormal tissue. The natural history of the disease is highly variable but malignant transformation is rare. There are salient histological, radiological, and clinical differences between lesions in the bones of the skull and those of the axial and appendicular skeleton [39]. This probably originates in the fact that the bones of the skull have a different embryological origin [40]. Radiographically, the bones of the skull are more likely to be sclerotic in appearance and those in the rest of the skeleton are more likely to be cystic and radiolucent. If long bone lesions tend to become quiescent after puberty (and this is debated), it is more certain that lesions in the skull do not. FD of the skull can be the cause of significant disfigurement and dysfunction. Computerized tomography, especially with 3D imaging, is the best modality for defining craniofacial bone disease.

The most extensive and thorough follow-up of polyostotic FD in patients with MAS included 15 patients [1]. Duration of FD ranged from 2 to 40 years. The most common presentations were pain, limp, or pathologic fracture and the most common site of FD was the base of the skull. Skull lesions were usually present at the time of diagnosis but were frequently asymptomatic. The impression was that FD continued to progress with time, with a more rapid course during the period of rapid linear growth. Worsening of FD during rapid growth is not confirmed by all investigators, but is generally felt to be the case by those clinicians who have cared for many patients.

The effect of concomitant hormonal status (either the normal hormonal changes of puberty, pregnancy, and menopause or the associated hypersecretory states of MAS) on the bone disease of MAS is not yet clear. While hyperthyroidism can advance the bone age in children, its effect on FD lesions is not known. In several patients worsening of FD has been reported with GH excess [32,41].

Indications for surgical treatment of FD include cranial nerve compression as manifested by loss of function or uncontrollable pain, nonunion of fractures, marked progressive deformity, and persistent pain from mechanical insufficiency. In general, the decision to operate to preserve cranial nerve function should be based on clinical and not radiographic findings. While acute visual loss requires aggressive neurosurgical intervention, it has become clear that prophylactic decompression of the optic nerve canal carries significant risk [42•,43,44]. Approaches to the surgical treatment of skeletal FD lesions, including curettage, bone grafting, and internal fixation, have been reviewed [45,46]. The strategy for management of FD requires ongoing monitoring and individualized care. Proliferation of residual mutant cells can cause recurrent disease.

To date, the only medical therapy that has shown any degree of efficacy is treatment with bisphosphonates. Bisphosphonates are a class of drugs that structurally mimic hydroxyapatite and are incorporated into bone. During bone resorption they are taken up by the osteoclast and the osteoclast is inhibited through mechanisms that include apoptosis induction and inhibition of protein prenylation [47]. There are three uncontrolled studies of the efficacy of the second generation bisphosphonate, pamidronate [48,49••,50]. They included a total of approximately 28 patients, but only six with MAS. The consistent findings were a decrease in bone pain and markers of bone turnover. Eleven of the 28 patients demonstrated changes in the appearance of the lesions on plain radiograph. Differential effects on skull versus long bone lesions, if any, were not addressed. A case report using a combination of pamidronate and alendronate [51] and other unpublished studies using pamidronate [52] have shown similar positive findings, but further research is needed [53]. Approaches for managing chronic pain in adult MAS patients is a topic that has not yet received adequate attention.

Skin

Cosmetic treatment of café-au-lait macules with a pigment-specific Q-switched ruby laser has been reported to produce variable results, with a recurrence rate of 40% to 50% [54,55].

Molecular pathophysiology

The three-dimensional structure of the activated form $G_s\alpha$ has recently been determined by itself and in complex with adenylyl cyclase [56,57]. As has been found with other α subunits, the conserved "arginine finger" at position 201 normally serves to facilitate GTP hydrolysis by stabilizing an enzymatic intermediate, and it is easy to understand why substitutions with Cys or His block GTPase activity and lead to constitutive signaling.

The traditional view is that G_s evokes its intracellular effects primarily through cAMP-mediated activation of

protein kinase A (PKA) and the subsequent phosphorylation of substrates that control diverse cellular phenomena such as metabolism, gene transcription, secretion, and cell proliferation. In addition, certain ion channels may be directly modulated by $G_S\alpha$ or by cAMP [58]. Phosphorylation of the nuclear transcription factor CREB by PKA leads to increased expression of genes containing cAMP-responsive elements, including early immediate genes such as the proto-oncogene c-*fos* [59,60]. A variety of experimental approaches have been undertaken to better understand how inappropriate activation of $G_S\alpha$ affects the development and function of different cell types *in vivo* and to define the specific signaling pathways involved.

Bone

An activating somatic mutation of $G_S\alpha$ with resultant elevation in intracellular cAMP could theoretically have effects on any of the major cells types in bone (osteoclast, osteoblast, osteocyte, and chondrocyte) and probably has effects, directly or indirectly, on all four. It is the combination of increased resorption of normal bone followed by the deposition of immature, disorganized fibro-chondro-osseous tissue that results in dysplastic lesions.

The effect of $G_S\alpha$ on cells of the osteoblastic lineage are the most studied and probably the most important. Investigation of tissue samples or osteoblastic cells derived from patients with MAS have demonstrated a number of abnormalities including: increased cAMP levels, increased proliferation rate, reduced production of osteocalcin (a late marker of osteoblast differentiation) [61•], increased levels of anti-adhesion bone matrix proteins versican and osteonectin, decreased levels of the pro-adhesion bone matrix proteins osteopontin and bone sialoprotein [62•], elevated levels of alkaline phosphatase [61•], increased expression of c-*fos* [6•], and increased interleukin-6 (IL-6) production [63]. The c-*fos* protein is a component of the AP-1 transcription factor and is known to play a role in mitogenesis and osteoblast differentiation. Because IL-6 is also involved in bone homeostasis [64], the elevated secretion of this cytokine by FD osteoblasts has been implicated in the pathogenesis of bone lesions. MC3T3-E1 mouse osteoblasts expressing mutant $G_S\alpha$ show increased production of IL-6, an effect that can be related to cAMP-mediated activation of multiple transcription factors (including CREB and AP-1) that bind to the IL-6 gene promoter [8••]. Similar mechanisms may be responsible for increased IL-6 production by cells in MAS. Increased IL-6 is unlikely to be responsible for the observed increase in osteoblastic cell proliferation in MAS, however, because IL-6 does not affect human osteoblastic cell growth *in vitro* [65]. In addition to the emerging role of c-*fos* and IL-6 in FD, it is possible that the recently described osteoprotegerin system [66,67], which is central to osteoclastogenesis and bone resorption, will also be implicated in FD pathophysiology.

An *in vivo* model for FD has recently been developed [12••]. It involves the implantation of bone-forming progenitor cells (bone marrow stromal cells) from patients with FD into immunocompromised mice. These cells differentiate and produce bone ossicles with many of the histological characteristics of human FD. This model holds great promise for advancing both our understanding of the pathophysiology and treatment of FD.

Endocrine

How cAMP affects the cell cycle machinery to either inhibit or induce cell proliferation in different systems is poorly understood [68,69,70••]. In many cells, including fibroblasts, cAMP inhibits cell growth and transformation induced by factors acting through receptor tyrosine kinases. In contrast, cAMP appears critical for stimulating the proliferation of many other types of cells, including the endocrine cells that are affected in MAS. Dog thyroid epithelial cells in primary culture represent one of the few model systems suitable for studying positive control of DNA synthesis by cAMP [69,70••]. Compared to known growth factor-stimulated pathways, it has become apparent that the cAMP-dependent mitogenic pathway in thyroid cells has several unusual characteristics. There is also evidence that components other than PKA are required for mediating the effects of cAMP [69]. The unique properties of this pathway may help explain how G_S stimulation of both mitogenesis and differentiated function are compatible in thyrocytes and other endocrine cells [70••].

The effect of continuous cAMP production on hormone secretion and proliferation of endocrine cells has also been analyzed by transfecting cell lines with activated $G_S\alpha$ mutants [30,59,71–73], by generating transgenic mice [28,29], and by studying the behavior of cells isolated from *gsp*-positive patients [15,33,74•,75]. It is important to remember that naturally occuring defects and experimental manipulations designed to raise intracellular cAMP may not always have equivalent effects [29,72,73]. Some cells expressing activated $G_s\alpha$ exhibit compensatory increases in cAMP degradation [71]. Human *gsp*-positive somatroph adenomas have recently been shown to exhibit a sevenfold increase in phosphodiesterase activity and a marked decrease in levels of $G_S\alpha$ protein compared to *gsp*-negative tumors, effects that might be expected to partially counteract constitutive activation of cAMP-dependent pathways [15,74•]. It remains to be seen whether compensatory feedback loops are activated in cells from MAS patients.

Invertebrate systems

Both the fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans* express homologs of several mammalian G protein subunits, including $G_s\alpha$, allowing detailed genetic analysis of highly conserved signal transduction pathways in these relatively simple organisms. Expression of constitutively activated $G_s\alpha$ in *Drosophila* wing epithelial cells at a specific stage in development induces wing blistering. This phenotype appears even in the complete absence of PKA activity, suggesting that a novel downstream effector may be involved [76]. A constitutively active form of $G_s\alpha$ results in neuronal degeneration in *C. elegans*, an effect that is suppressed by second site mutations in a gene that encodes an adenylyl cyclase [77,78]. Other genetic loci that suppress or diminish the effects of activated $G_s\alpha$ have also been isolated. Cloning these components may provide additional insights into the molecular pathophysiology of MAS, and possibly suggest additional targets for therapeutic intervention in humans.

Recent discoveries

A novel family of cAMP-binding proteins that have recently been cloned [79,80] may help explain the PKA-independent effects of $G_s\alpha$ observed in several of the model systems described above [58,69,76]. These proteins act as direct guanine nucleotide exchange factors for Rap1, a ubiquitously expressed member of the Ras superfamily of small GTPases, and do not require the presence of PKA. Although the precise function of Rap1 is not yet known, traditional concepts of cAMP-mediated regulation of growth and differentiation may need to be revised.

Heterozygous inactivating mutations of the $G_s\alpha$ gene are known to cause pseudohypoparathyroidism (PHP) type Ia. Recent investigation of the inheritance patterns of different forms of PHP [81], study of tissue-specific effects in $G_s\alpha$ knockout mice [82••], and examination of multiple mRNAs transcribed from the $G_s\alpha$ gene suggest that this is an imprinted gene of "bizarre complexity" [83•]. The implications this has for MAS remain to be defined, but it is possible that pathological effects in some tissues may be dependent on which parental allele bears the mutation [82••].

Conclusions

The discovery of Arg^{201} $G_s\alpha$ gene mutations in MAS represents only the first step in understanding the pathogenesis of this complex disorder. Efforts are now underway to identify the key functional target genes that are activated by $G_s\alpha$ in bone and other affected tissues. The assumption that mutational effects of $G_s\alpha$ are always mediated by cAMP activation of PKA needs to be re-evaluated. Understanding the characteristics which distinguish cAMP-mediated mitogenic pathways from those triggered by tyrosine kinase receptors and other proliferative agents may suggest unique avenues for therapeutic intervention that will allow the specific targeting of abnormal cells.

In MAS, much of the observed heterogeneity in clinical presentation has been attributed to variation in the number and distribution of cells carrying an Arg^{201} mutation. The role of additional genetic mutations, gene imprinting, and environmental mechanisms has not yet been investigated. There is a critical need for more clinical data on the natural history of MAS, especially during adolescence and adult life. The use of bisphosphonates shows promise as a new medical treatment for the disabling bone disease of MAS, but more study is needed.

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